REMARKS

Status of the claims

Claims 67 and 70-73 are allowed. Claims 1-3, 46-51, and 74-81 are under consideration in this application. Claims 1-3, 46-51, and 74-81 are rejected and claims 80 and 81 are objected to.

The 35 U.S.C. §112, first paragraph rejections

(a) Claims 1-3, 78, and 79 stand rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

From the comments on page 3, lines 1-3, of the Office Action, Applicants understand the Examiner's position to be that the specification does not support the phrase "conservative amino acid substitutions". While disagreeing with this position, in order to expedite prosecution of the instant application, Applicants have deleted the limitation in claim 1 containing the phrase and further amended the claim in order to conform it to the deletion.

From the comments on page 3, lines 4-9, of the Office Action, Applicants understand the Examiner's position to be that the specification does not support the phrase "SSC at a concentration not greater than 0.5 x". While disagreeing with this position, in order to expedite prosecution of the instant application, Applicants have replaced this phrase in claims 2 and 3 with the phrase "SSC at a concentration between 0.05 x and 0.5 x". This amendment is supported by the specification, e.g., at page 7, line 13.

(b) Claims 46-51 and 74-77 stand rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

From the comments on page 3, line 14, to page 6, line 2, of the Office Action, Applicants understand the Examiner's position to be that specification does support the claims commensurate with their scope. While not agreeing with this position, in order to expedite

prosecution of the instant application, Applicants have amended claims 46 and 51 by incorporating the limitations of claims 80 and 81, respectively, and have cancelled claims 80 and 81. Applicants submit that, in light of these amendments, the rejection is moot. The Examiner stated that incorporating the limitations of claims 46 and 51 (and all intervening claims) into dependent claims 80 and 81, respectively, would render claims 80 and 81 allowable (Office Action, page 9, lines 7-9). There being no such intervening claims, this statement indicated the Examiner's belief that the amendments made herein (the converse of those he suggested but having the same result) would put claims 46 and 51 in condition for allowance.

In light of the above considerations, Applicants request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 46-51 and 74-77 stand rejected as allegedly being unpatentable over Stanton et al., 1992, Galili, and Hodges et al. Applicants respectfully traverse this rejection.

From the comments on page 8, line 4, to page 9, line 5, of the Office Action, Applicants understand the Examiner's position to be that: (1) the combination of Stanton et al. and Galili et al. teaches making the DNA construct of claim 46 and the method of claim 51; and (2) these two references combined with Hodges et al. teaches the DNA construct and method in which the DNA construct contains a FRT site and/or a neo^R gene. Applicants disagree with this position. Stanton et al. discloses generally methods of generating "knockout" mice and makes no mention of α-galactosyltransferase genes. Galili et al. makes a broad, non-specific statement regarding the problem of α-galactosyl epitopes in xenotransplantation that includes the suggestion of using knockout technology. However, Galili expresses skepticism as to the success of such an approach and concludes that "an attempt to inactivate α1,3GT may be warranted." (page 482, column 1, last paragraph; emphasis added). Thus Galili's enthusiasm regarding the success of the knockout approach can fairly be characterized as luke warm and his disclosure is at best an invitation to try without the least assurance of success. The Hodges et al. reference teaches generally the technology of DNA constructs containing a FRT site (e.g., column 5, line 33 to column 6, line 17), various maize protein-encoding sequences, (Examples 1-4), and a selectable marker gene (Example 3); the reference makes no mention of knockout animals and, in particular

no mention of animals with disrupted α-galactosyltransferase genes. Thus, the cited references, either singly or in combination, do not contain the requisite motivation to combine their disclosure and thus to knock out an α-galactosyltransferase gene. In addition, the references contain no suggestion of knocking out an α-galactosyltransferase gene that, prior to disruption, encodes a porcine α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10, as is required by claims 46 and 51.

In light of the above considerations, Applicants respectfully submit that the cited art does not render the above-listed claims obvious and request thus that the rejections under 35 U.S.C. §103(a) be withdrawn.

The claim objections

Claims 80 and 81 stand objected to as allegedly being dependent upon a rejected base claim. Applicants respectfully submit that the objections are moot in light of the incorporation of the limitations of dependent claims 80 and 81 into claims 46 and 51, respectively, and the cancellation of claims 80 and 81.

CONCLUSIONS

Applicants submit that claims 1-3, 46-51, 67, and 70-79 patentably define the invention. Applicants request that the Examiner reconsider the rejections set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a petition for an automatic extension of time with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 12/4/01

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Version with markings to show changes made

In the claims:

Claims 80 and 81 have been cancelled.

Claims 1-3, 46, and 51 have been amended as follows:

1. (Four times amended) A purified and isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of (1) nucleotides 90 -1203 of the porcine nucleic acid sequence with SEQ ID NO: 7, (2) a sequence encoding a porcine polypeptide having α-1,3 galactosyltransferase activity and having the amino acid sequence of SEQ ID NO:10, [(3) a sequence that encodes a second polypeptide identical to said porcine polypeptide except for one or more conservative amino acid substitutions, wherein said second polypeptide retains a functional α-1,3 galactosyltransferase catalytic site, a functional membrane anchor domain and a functional stem region,] and [(4)] (3) a sequence complementary to the sequence of (1)[,] or (2) [or (3)].

2. (Twice amended) A host cell that is transformed with a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of (1) nucleotides 90 - 1203 of the porcine nucleic acid sequence with SEQ ID NO: 7, (2) a sequence corresponding to the sequence of (1) within the scope of the degeneracy of the genetic code, (3) a sequence that encodes a porcine polypeptide having α-1,3 galactosyltransferase activity and that hybridizes with a sequence complementary to the sequence of (1) or (2) after a wash at 65°C in a buffer containing 0.1% SDS and SSC at a concentration [not greater than] between 0.05 x and 0.5 x , and (4) a sequence complementary to the sequence of (1), (2) or (3).

3. (Twice amended) A porcine α-1,3 galactosyltransferase encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of (1) nucleotides 90 -1203 of the porcine nucleic acid sequence with SEQ ID NO: 7, (2) a sequence corresponding to the sequence of (1) within the scope of the degeneracy of the genetic code, (3) a sequence that encodes a porcine polypeptide having α-1,3 galactosyltransferase activity and that hybridizes with a sequence complementary to the sequence of (1) or (2) after a wash at 65°C in a

buffer containing 0.1% SDS and SSC at a concentration [not greater than] between 0.05 x and 0.5 x, and (4) a sequence complementary to the sequence of (1), (2) or (3).

46. (Thrice amended) A DNA construct comprising a disrupted porcine α-1,3 galactosyltransferase gene, wherein the disruption is by insertion of an exogenous sequence into said gene such that the disruption prevents expression of functional α-1,3 galactosyltransferase, wherein the gene, prior to disruption, encodes a porcine α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10.

51. (Amended) A method for generating a porcine cell comprising at least one inactivated α-1,3 galactosyltransferase gene, the method comprising:

(a) providing a plurality of porcine cells;

(b) introducing into said cells the DNA construct of claim 46;

(c) incubating said cells such that homologous recombination occurs between the chromosomal sequence encoding α-1,3 galactosyltransferase and the introduced DNA construct comprising the disrupted α-1,3 galactosyltransferase gene; and

(d) identifying a porcine cell comprising at least one inactivated α-1,3 galactosyltransferase gene,

wherein the gene, prior to disruption, encodes a porcine α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10.